DOXORUBICIN CARDIOTOXICITY IN AFRICAN AMERICANS

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Purpose: The African-American race was examined as a risk factor for cardiotoxicity from doxorubicin-based therapy for cancer.

Patients and Methods: Retrospective survey of the Howard University Hospital cancer registry during 1997–2001 identified 100 evaluable patients out of 120 African Americans who underwent doxorubicin-based combination chemotherapy (65% women, 35% men, median age 46 years, range 32–84 years). The fraction of patients who developed post-treatment cardiotoxicity, defined as congestive heart failure or a left-ventricular ejection fraction less than 45%, was compared with that from a retrospective study of 399 patients of unknown age and racial distribution. Cases were stratified by cumulative dose of doxorubicin. Statistical significance of the difference in incidence of cardiotoxicity was tested by chi-square analysis.

Results: Patients received multiple doses of doxorubicin (range 264 to 580 mg/m^2 with median of 374) with the final echocardiographic assessment at a median of 1.3 years. Howard oncologists frequently used a 48-hour infusion rather than the conventional rapid bolus to reduce the cardiotoxicity of doxorubicin. The fraction with cardiotoxicity in our study versus Lefrak's review at four ranges of doxorubicin was 25% versus 18% at 551–600 mg/m^2, 10% versus 4% at 501–550 mg/m^2, 4% versus 1% at 451–500 mg/m^2, and 0% versus <1% at <450 mg/m^2. Seventy-two percent of the patients having depressed ejection fraction and/or heart failure were women. African Americans had a higher rate of cardiotoxicity after doxorubicin (7/100 cases) than that of Lefrak's (10/399) study population and were statistically significant at $p<0.027$ with an odds ratio of 2.93.

Conclusion: We have shown for the first time that African Americans at our institution appear to suffer cardiotoxicity from doxorubicin three times more frequently than the previously noted study population. To better clarify this observation, a larger study in a multiracial setting is needed.(*J Natl Med Assoc.* 2004;96:196–199.)

Key words: doxorubicin ♦ cardiotoxicity ♦ African Americans

INTRODUCTION

In 1957 streptomyces peucetius was isolated from southern Italian soil. The compound 1, 4-hydroxydaunomycin was produced by a variant strain and called Adriamycin (Adria) because of the proximity of the parent strain source to Adriatic Sea[1]. Doxorubicin hydrochloride, the generic name for Adriamycin, has a leading role in the treatment of hematological malignancies and solid tumors. It is the single most active agent for the treatment of most types of lymphoma in the "CHOP" regimen and for metastatic breast cancer in the "CAF" or "CA" regimens). These regimens ordinarily require 300–400 mg/m^2 of doxorubicin for CHOP, 240 mg/m^2 for CA, and 240–300 mg/m^2 for CAF.

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Doxorubicin may produce early or late cardiotoxic reactions[2]. Early effects include: a) pericarditis–myocarditis; b) significant arrhythmias especially, AV conduction block, and ventricular arrhythmia; and c) sudden onset of left ventricular dysfunction presenting as acute cardiac failure. These early cardiac effects are idiosyncratic, apparently independent of dose and very rare. Late cardiac effects are common dose-dependent loss of left ventricular function, presenting as congestive heart failure (CHF). While the time of presentation can vary from weeks to years after receiving doxorubicin, risk correlates well with cumulative dosing, with risks of 5% at 400 mg/m^2 of body surface area and a greater-than-linear progression above this level. Although there are no reports in the literature of risk related to African race, oncologists at Howard University Hospital have long regarded African Americans as having a higher risk of doxorubicin cardiotoxicity based upon their undocumented experience.

Most African-American patients at Howard have received doxorubicin as a 48-hour infusion rather than the usual bolus over 30–60 minutes, a measure which should reduce the frequency of cardiotoxicity by 43%. In addition, it is well known that African Americans have a higher prevalence and earlier onset of cardiovascular diseases, hypertension, and atherosclerosis. The aim of the present study was to examine African-American race as a risk factor for cardiotoxicity from doxorubicin-based therapy for cancer.

PATIENTS AND METHODS

A retrospective survey of the Howard University Hospital cancer registry during 1997–2001 was conducted to identify all patients who underwent Adriamycin-based combination chemotherapy. Charts were reviewed to find evaluable patients who had records of the cumulative dose of doxorubicin and assessment of clinical cardiac status and echocardiogram both before therapy and at one- to four years post-therapy. Post-treatment cardiotoxicity was defined as CHF, or a measured left ventricular ejection fraction less than 45%. The fraction of patients who developed cardiotoxicity at Howard was compared with that from a retrospective study of 399 patients, whose exact age and racial composition were unknown[3,4]. Statistical significance of the difference in incidence of cardiotoxicity was tested by chi-square analysis. Cases were stratified by cumulative dose of doxorubicin, and the frequencies at each dosing level were compared between our cases and the cases mentioned in the previous study by Lefrak et al.[4]

RESULTS

Out of 120 eligible patients receiving doxorubicin combination therapy at Howard during the study period, 100 patients were evaluable, all of whom were African American (65% women, 35% men, median age 46 years, range 32–84 years). Fifteen patients had hypertension, and 10 were diabetics. None of the patients had history of CHF or coronary artery disease before the institution of chemotherapy. Patients received multiple doses of doxorubicin (range 264–580 mg/m^2 with median of 374 mg/m^2) with the final echocardiographic assessment at a median of 1.3 years (Table 1). The fractions with cardiotoxicity in our study versus those from Lefrak's study were 25% versus 18% at 551–600 mg/m^2, 10% versus 4% at 501–550 mg/m^2, 4% versus 1% at 451–500 mg/m^2, and 0% versus <1% at <450 mg/m^2 cumulative dose of doxorubicin. Lumping all levels of exposure, African Americans in our study had a higher rate of cardiotoxicity after doxorubicin (7/100 cases) than the study population in Lefrak's study (10/399), a difference statistically significant at $p<0.027$ with an odds ratio of 2.93 (95% confidence interval from 0.98 to 8.6). Gender did not appear to be a significant risk factor within our case series. There were 65 women out of 100 patients. Five out of seven patients who developed cardiotoxicity ($p<0.3$ for the chi-square test) were women. In our case series, 59% of treatments with doxorubicin were for breast cancer of which five patients developed cardiotoxicity, 36% for lymphoma of which two developed cardiotoxicity, and 5% for other malignancies, with none exhibiting cardiotoxicity.

DISCUSSION

Late cardiotoxic effects of doxorubicin are an increasing problem for large numbers of patients who survive cancer. This cardiotoxicity is often progressive and disabling. In a retrospective study of 399 patient records, CHF and cardiomyopathy were found to be dose-dependent, and the incidence of these complications increased considerably when the cumulative dose of the drug exceeded 400 mg per square meter of body-surface area[4,5]. Several risk factors have been recognized for doxorubicin-induced cardiomyopathy: age >70 years[6,7], combination chemotherapy[6], previous or concomitant mediastinal

Table 1. Clinical characteristics of Seven Patients Who

Patient Number	Age (Years)/ Gender	Type of Cancer/ Comorbid Conditions	Radiation
1	54/ F	Breast cancer/hypertension	Y
2	48/F	Breast cancer	Y
3	56/F	Breast cancer/arthritis	N
4	82/M	Non-Hodgkin's lymphoma/hypertension	N
5	69/M	Non-Hodgkin's lymphoma	N
6	34/F	Breast cancer	N
7	46/F	Breast cancer/asthma	Y

radiotherapy[7], underlying cardiac disease[7], hypertension[7], and liver disease[8]. To our knowledge, race has not previously been reported as a significant risk factor of doxorubicin cardiotoxicity. It is, therefore, important that we identified a nearly three-fold greater rate of this cardiotoxicity in our population of African-American patients in comparison with earlier studies with unknown racial distribution.

While African race is a risk factor for hypertensive and atherosclerotic cardiovascular disease, this risk would be approximately 1.25- to 1.3-fold at the median age of our study population (46 years). Therefore, it is unlikely that most of this increased risk was due to concurrent cardiovascular disease.

The major limitations of this study are its relatively small size and the lack of concurrent patients treated at the same institution who were not African. We plan to embark on retrospective and prospective surveillance of doxorubicin toxicity within institutions with multiracial cancer patient populations.

It is particularly disturbing that such a high risk of cardiotoxicity was found among a cancer practice in which there has been a strong tradition to protect African-American patients from doxorubicin cardiotoxicity by utilizing long infusion times (two to four days) or immediate pretreatment with dexrazoxane. Our study serves to emphasize the limitations of most prior studies which largely recruited caucasian patients. We suspect that the true risk of this toxicity among African Americans might be 40% greater than estimated from this study, assuming that longer infusions or use of dexrazoxane have

Developed Adriamycin-Induced Cardiomyopathy

Treatment	Total Dose of Adriamycin mg/m^2	Cardiac Status (EF%) Pretreatment	Cardiac Status (EF%) Post-Treatment
Adriamycin + cyclophosphamide	472	55%	<40%
Adriamycin + cyclophosphamide	460	60%	40–45%
Cyclophosphamide+adriamycin+ 5-fluorouracil	520	55%	35%
CHOP	510	48%	<20%
CHOP	580	55%	15%
Cyclophosphamide+adriamycin+ 5-fluorouracil	480	60%	40%
Adriamycin + cyclophosphamide	518	>55%	40%

a similar protective effect among African Americans as among caucasians. A direct test of this hypothesis is urgently needed.

CONCLUSION

We have shown for the first time that African Americans appear to suffer cardiotoxicity from doxorubicin three times more frequently than the previously mentioned study population. This observation is particularly disturbing since most of our patients received protective measures thought to reduce this cardiotoxicity by 40–50% in contrast to those of the non-African control group. A larger study in a multiracial setting is needed to clarify this observation. This data, because of the numbers involved and lack of head-to-head comparison cannot be definitive.

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